Common variant in myocilin gene is associated with high myopia in isolated population of Korcula Island, Croatia

doi: 10.3325/cmj.2009.50.17

Common Variant in Myocilin Gene Is Associated with High Myopia in Isolated Population of Korčula Island, Croatia

Aim To study the association between genetic variants in myocilin and collagen type I alpha 1 genes and high myopia in an isolated island population.

Methods A total of 944 examinees from the genetic epidemiology study conducted on the island of Korčula, Croatia, were included in the study. We selected 2 short nucleotide polymorphisms (SNP) available in our genome-wide scan set of SNPs that were previously associated with high myopia and used them to replicate previous claims of possible association.

Results Nineteen cases of high myopia, defined as the refraction of ≤-6.00 diopters, were identified and included in the analysis. We showed that rs2075555 in the *COL1A1* gene was not associated with high myopia. In contrast, rs2421853 in the myocilin gene was significantly associated in both bivariate ($P=0.006$) and age- and sex-adjusted analysis ($P=0.049$).

Conclusion Myocilin seems to be a very strong candidate for explaining some of the pathophysiological pathways leading to the development of both glaucoma and high myopia. As our finding was obtained in a relatively underpowered sample, further research and replication of these results is needed.

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Received: December 16, 2008

Accepted: January 23, 2009

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Individual variation in eye morphometry traits is responsible for numerous ocular conditions, ranging from mild refractive errors to potentially vision-threatening diseases such as macular degeneration and glaucoma (1,2). It is estimated that a half of the United States population aged 20 and older is affected by clinically important refractive conditions, myopia or hyperopia (3). Among ocular morphometric traits, axial length is considered to be the most important determinant of refraction (4).

Both environmental and genetic factors have been shown to affect the development of refractive errors. Sudden increase in the prevalence of myopia, especially in Asian countries, where up to 90% of young adults are affected, suggests possible environmental or behavioral causes (5,6). However, twin studies demonstrated genetic effect and showed that heritability of refractive error and axial length is high, reaching up to 94% (7,8).

High myopia, defined as refraction of ≤-6.00 diopters (9), has been associated with various adverse effects and is a frequent cause of legal blindness, especially in younger patients, due to macular degeneration, glaucoma, or retinal detachment (1,2,10,11). This creates a considerable socioeconomic burden for the affected individuals and their families (12). Several possible variants determining high myopia have been discovered, with rather variable results among different populations (13-15). One of such genes is myocilin gene, which was already associated with both juvenile open angle glaucoma and primary open angle glaucoma (16-18). Another is the collagen type I alpha 1 (COL1A1) gene on the chromosome 17q22-q23.3, which has been found to be implicated in pathogenesis of high myopia in the Japanese population (19).

Axial length is the most important determinant of refractive error, which has been associated with chromosome 2p24 in the isolated Sardinian population (20). Suggestive linkage of axial length to chromosome 5q has also been described (21). Both of these studies used genome-wide scans based on very scarcely distributed microsatellite markers. On the other hand, more recent genome-wide association studies have used SNPs as a tool for gene mapping, allowing much denser genome-wide scans and finer mapping (22).

The genetic epidemiology research program in Croatian island isolates began in 1999 (23,24), was expanded to study human genetic variation and the effects of isolation and inbreeding (25-33), and later broadened its focus to include diseases and gene mapping studies (34-41). By now, the research project has included more than 3000 examinees from isolated populations and aims to eventually reach 10 001 of them.

The aim of this study was to investigate the reported association between two genomic SNP markers, representing genetic variants in the *COL1A1* and myocilin gene, and high myopia, using the genetic epidemiology resource from the isolated population of the Island of Korčula, Croatia.

MATERIALS AND METHODS

This study included adult inhabitants of the Korčula Island, Croatia. The participants were recruited from general practitioners' records. Also, we tried to increase the number of participants by making invitations through radio announcements, personal contacts, postal service, and e-mail. All examinees were aged 18 or more and had signed an informed consent. The study was approved by the Ethical Committee of the School of Medicine, University of Zagreb, Croatia.

Refraction data were obtained by using automated keratorefractometer (Nidek ARK-30, Nidek S.A., Créteil, France), with examinees in a supine position. After keratorefractometry, one drop of 0.5% tetracaine hydrochloride (Tetrakain, Pliva, Zagreb, Croatia) was instilled in each eye to anesthetize corneal surface. Axial length was measured by A-scan ultrasound (Nidek Echoscan US-1800, Nidek S.A.). High myopia was defined as the refraction of≤-6.00 diopters (using spherical equivalent, defined as the sum of spherical power and half of cylindrical refraction power, where values between -6 and -17 were classified as high myopia). Examinees with the required refraction in either eye were considered to have high myopia. History of cataract surgery (n = 34), retinal detachment (n = 7), or other ocular conditions influencing refraction (n = 11) were the exclusion criteria. A total of 969 examinees were recruited in the field work. All examinees provided a sample of blood, which was centrifuged on the spot and leukocytes were isolated and used for the DNA extraction. DNA extraction was performed using Qiagen kit (Tepnel, Manchester, UK). A total of 944 examinees were genotyped using Sentrix® HumanHap Genotyping BeadChip, version 2 (Illumina Inc, San Diego, CA, USA).

The data are presented as percentages for categorical variables and medians with interquartile ranges for numerical variables. Categorical data were analyzed using Fisher ex-

TABLE 1. Descriptive statistics for right and left eye spherical and cylindrical power in the Korčula island sample

Parameter	Sex differences (median, interquartile range)		Correlation with age		
	Men	Women	*P**	Correlation coefficient	*P*†
Right eye spherical power	-0.37 (1.49)	-0.12 (1.62)	0.025	0.33	<0.001
Right eye cylindrical power	0.37 (0.87)	0.37 (0.63)	0.502	0.25	<0.001
Left eye spherical power	-0.25 (1.81)	-0.12 (1.75)	0.489	0.35	<0.001
Left eye cylindrical power	0.37 (0.87)	0.37 (0.63)	0.852	0.22	<0.001

*Mann-Whitney test.
†Spearman rank test.

act test. Two groups of numerical data were analyzed with Mann-Whitney test, while Spearman rank test was used in the correlation analysis. Also, multivariate analysis (logistic regression) was performed with age and sex as covariates. All analyses were performed in the SPSS, version 13 (SPSS Inc, Chicago, IL, USA), with $P<0.05$ as the level of statistical significance.

RESULTS

In our participants, median values of right and left spherical and cylindrical power showed certain level of sex effect (right eye spherical power) and a correlation with age (Table 1). Among 944 examinees, 19 had the diagnosis of high myopia. There were 4 men (21%) and 15 women (79%) with high myopia, but this difference was not significant ($P=0.173$, Fisher exact test).

The rs2421853 in myocilin gene was significantly associated with high myopia in the bivariate analysis, while rs2075555 in the *COL1A1* gene was not (Table 2). Finally, the first SNP maintained significance in the logistic regression model, after adjusting for the effects of age and sex (Table 3). Within this SNP, AA increased the risk of having high myopia almost five times, compared with AG and GG, which had a protective effect (Table 3). This SNP explained a total of 2.5% of variance (Nagelkerke $R^2=0.025$).

TABLE 2. Sample breakdown according to the short nucleotide polymorphisms (SNP) and presence or the absence of high myopia

SNP	No. (%) of subjects			*P**
	without high myopia	with high myopia	total	
rs2421853				
AA	44 (5.2)	3 (19)	47 (5.5)	0.006
AG	296 (35)	3 (19)	299 (35)	
GG	504 (60)	10 (63)	514 (60)	
total	844 (100)	16 (100)	860 (100)	
rs2075555				
AA	19 (2.4)	0 (0)	19 (2.3)	0.137
AG	210 (26)	5 (29)	215 (27)	
GG	565 (71)	12 (71)	577 (71)	
total	794 (100)	17 (100)	811 (100)	

*Fisher exact test.

TABLE 3. The age- and sex-adjusted effects of the short nucleotide polymorphisms (SNP) rs2421853 (myocilin gene) on the high myopia (logistic regression)

Variable	*P*	Odds ratio (95% confidence interval)
Age	0.443	0.99 (0.95-1.02)
Sex		
men (Ref.)		1.00
women	0.38	1.68 (0.53-5.33)
rs2421853		
AA (Ref.)	0.049	1.00
AG	0.017	0.14 (0.03-0.70)
GG	0.050	0.26 (0.07-0.99)

DISCUSSION

This study identified a common SNP in myocilin gene as the genetic variant that confers strong risk of high myopia in the isolated population sample of the island of Korčula. Previous studies have so far identified a number of potential candidate genes which determine high myopia, including *COL1A1* (19), *COL2A1* (42), lumican (43), *EGR1* (44), and myocilin (18). We selected two SNPs available in our genome-wide scan set of SNPs that were previously associated with high myopia and used them in this analysis to replicate previous claims of possible association. We replicated the results for myocilin variant, but not for *COL1A1* variant.

The myocilin gene, located on chromosome 1q24-q25, encodes a myocilin protein, which has been associated with cytoskeletal function. It is expressed in many tissues, most notably in the ciliary body, iris, trabecular meshwork, sclera, choroid, and retina (45). Mutations in the myocilin gene were found in patients with open angle glaucoma, but also in patients with other types of glaucoma, such as normal tension, pigmentary, and exfoliation glaucoma (46). Myopia is a known risk factor for open angle glaucoma and myopic eyes frequently exhibit higher intraocular pressure in comparison with emmetropic eyes (47-51). Thus, our study showed that variants in myocilin gene may be one of the common etiological factors linking the high myopia and open angle glaucoma.

Tang et al showed that myocilin polymorphisms have been associated with high myopia in the Chinese population (18). Association was shown for SNP rs2421853 and SNP rs235858, with the latter showing higher degree of significance. Linkage studies have connected chromosomes 2q, 3q26, 4q, 7q, 10q, 12q, 17q, 18p, and 22q and high myopia (50-58). However, all these reports need to be taken with a great deal of caution because it is likely that most historic genome-wide scans based on STR markers and linkage approach were underpowered to detect true effects and also very prone to false-positive findings. Even though several studies analyzed isolated populations, none of them has shown a linkage to myocilin (54,58). In our study population, we replicated the effect of SNP rs2421853, but not of the SNP rs235858. Despite the fact that the study by Tang et al was a family-based association study with 557 members from 162 nuclear families, with at least one offspring with high myopia and that our study was population-based, we were able to demonstrate the value of population isolates in detecting loci for complex diseases. Furthermore, the results of this study show relatively high percent of variance explained (2.5%), making this gene an even more likely candidate for further functional research and sequencing.

The limitations of this study include the small number of cases (only 19). Also, we were able to study only two implicated SNPs available in our genome-wide scan, although the trait we wanted to explain was highly complex (59). One of the best strategies to further investigate this finding would be to substantially increase statistical power, either by increasing the number of examinees (what would not be very feasible in the population genetic cross-sectional approach) or by performing case-control study of high myopia. The best approach would be to combine the results from several studies and perform a large-scale meta-analysis of published and unpublished studies on both the genetic markers and ophthalmological measurements. Approaches such as Mendelian randomization (60) could further reduce the chances of spurious associations. However, the finding of a biologically highly plausible candidate gene in the investigated population is encouraging and warrants further research on the role of myocillin in high myopia etiology.

References

1 Cohen SY, Laroche A, Leguen Y, Soubrane G, Coscas GJ. Etiology of choroidal neovascularization in young patients. Ophthalmology. 1996;103:1241-4. Medline:8764794

2 Mitchell P, Hourihan F, Sandbach J, Wang JJ. The relationship between glaucoma and myopia: the Blue Mountains Eye Study. Ophthalmology. 1999;106:2010-5. Medline:10519600 doi:10.1016/S0161-6420(99)90416-5

3 Vitale S, Ellwein L, Cotch MF, Ferris FL III, Sperduto R. Prevalence of refractive error in the United States, 1999-2004. Arch Ophthalmol. 2008;126:1111-9. Medline:18695106 doi:10.1001/archopht.126.8.1111

4 Kinge B, Midelfart A, Jacobsen G, Rystad J. Biometric changes in the eyes of Norwegian university students–a three-year longitudinal study. Acta Ophthalmol Scand. 1999;77:648-52. Medline:10634556 doi:10.1034/j.1600-0420.1999.770608.x

5 Saw SM, Katz J, Schein OD, Chew SJ, Chan TK. Epidemiology of myopia. Epidemiol Rev. 1996;18:175-87. Medline:9021311

6 Park DJ, Congdon NG. Evidence for an "epidemic" of myopia. Ann Acad Med Singapore. 2004;33:21-6. Medline:15008557

7 Hammond CJ, Snieder H, Gilbert CE, Spector TD. Genes and environment in refractive error: the twin eye study. Invest Ophthalmol Vis Sci. 2001;42:1232-6. Medline:11328732

8 Dirani M, Chamberlain M, Shekar SN, Islam AF, Garoufalis P, Chen CY, et al. Heritability of refractive error and ocular biometrics: the Genes in Myopia (GEM) twin study. Invest Ophthalmol Vis Sci. 2006;47:4756-61. Medline:17065484 doi:10.1167/iovs.06-0270

9 Hofstetter H, Griffin J, Berman M, Everson R. Dictionary of visual science and related clinical terms. 5th ed. Boston (MA): Butterworh-Heinmann; 2000.

10 Burton TC. The influence of refractive error and lattice degeneration on the incidence of retinal detachment. Trans Am Ophthalmol Soc. 1989;87:143-55. Medline:2562517

11 Xu L, Wang Y, Li Y, Wang Y, Cui T, Li J, Jonas JB. Causes of blindness and visual impairment in urban and rural areas in Beijing: the Beijing Eye Study. Ophthalmology. 2006;113:1134.e1-11. Medline:16647133

12 Jacobi FK, Zrenner E, Broghammer M, Pusch CM. A genetic perspective on myopia. Cell Mol Life Sci. 2005;62:800-8. Medline:15868405 doi:10.1007/s00018-004-4353-z

13 Paluru PC, Nallasamy S, Devoto M, Rappaport EF, Young TL. Identification of a novel locus on 2q for autosomal dominant high-grade myopia. Invest Ophthalmol Vis Sci. 2005;46:2300-7. Medline:15980214 doi:10.1167/iovs.04-1423

14 Zhang Q, Guo X, Xiao X, Jia X, Li S, Hejtmancik JF. A new locus for autosomal dominant high myopia maps to 4q22-q27 between D4S1578 and D4S1612. Mol Vis. 2005;11:554-60. Medline:16052171

15 Nallasamy S, Paluru PC, Devoto M, Wasserman NF, Zhou J, Young TL. Genetic linkage study of high-grade myopia in a Hutterite population from South Dakota. Mol Vis. 2007;13:229-36. Medline:17327828

16 Alward WL, Fingert JH, Coote MA, Johnson AT, Lerner SF, Junqua D, et al. Clinical features associated with mutations in the chromosome 1 open-angle glaucoma gene (GLC1A). N Engl J Med. 1998;338:1022-7. Medline:9535666 doi:10.1056/NEJM199804093381503

17 Zgaga L, Hayward C, Vatavuk Z, Bencic G, Zemunik T, Valkovic A, et al. High prevalence of glaucoma in Veli Brgud, Croatia, is caused by a dominantly inherited T377M mutation in the MYOC gene. Br J Ophthalmol. 2008;92:1567-8. Medline:18952665 doi:10.1136/bjo.2008.143552

18 Tang WC, Yip SP, Lo KK, Ng PW, Choi PS, Lee SY, et al. Linkage and association of myocilin (MYOC) polymorphisms with high myopia in a Chinese population. Mol Vis. 2007;13:534-44. Medline:17438518

19 Inamori Y, Ota M, Inoko H, Okada E, Nishizaki R, Shiota T, et al. The COL1A1 gene and high myopia susceptibility in Japanese. Hum Genet. 2007;122:151-7. Medline:17557158 doi:10.1007/s00439-007-0388-1

20 Biino G, Palmas MA, Corona C, Prodi D, Fanciulli M, Sulis R, et al. Ocular refraction: heritability and genome-wide search for eye morphometry traits in an isolated Sardinian population. Hum Genet. 2005;116:152-9. Medline:15611866 doi:10.1007/s00439-004-1231-6

21 Zhu G, Hewitt AW, Ruddle JB, Kearns LS, Brown SA, Mackinnon JR, et al. Genetic dissection of myopia: evidence for linkage of ocular axial length to chromosome 5q. Ophthalmology. 2008;115:1053-7. Medline:17964656 doi:10.1016/j.ophtha.2007.08.013

22 Barrett JC, Hansoul S, Nicolae DL, Cho JH, Duerr RH, Rioux JD, et al. Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease. Nat Genet. 2008;40:955-62. Medline:18587394 doi:10.1038/ng.175

23 Rudan I. Inbreeding and cancer incidence in human isolates. Hum Biol. 1999;71:173-87. Medline:10222641

24 Rudan I, Campbell H, Rudan P. Genetic epidemiological studies of eastern Adriatic Island isolates, Croatia: objective and strategies. Coll Antropol. 1999;23:531-46. Medline:10646227

25 Wright A, Charlesworth B, Rudan I, Carothers A, Campbell H. A polygenic basis for late-onset disease. Trends Genet. 2003;19:97-106. Medline:12547519 doi:10.1016/S0168-9525(02)00033-1

26 Vitart V, Biloglav Z, Hayward C, Janicijevic B, Smolej-Narancic N, Barac L, et al. 3000 years of solitude: extreme differentiation in the island isolates of Dalmatia, Croatia. Eur J Hum Genet. 2006;14:478-87. Medline:16493443 doi:10.1038/sj.ejhg.5201589

27 Carothers AD, Rudan I, Kolcic I, Polasek O, Hayward C, Wright AF, et al. Estimating human inbreeding coefficients: comparison of genealogical and marker heterozygosity approaches. Ann Hum Genet. 2006;70:666-76. Medline:16907711 doi:10.1111/j.1469-1809.2006.00263.x

28 Rudan I, Smolej-Narancic N, Campbell H, Carothers A, Wright A, Janicijevic B, et al. Inbreeding and the genetic complexity of human hypertension. Genetics. 2003;163:1011-21. Medline:12663539

29 Rudan I, Biloglav Z, Vorko-Jovic A, Kujundzic-Tiljak M, Stevanovic R, Ropac D, et al. Effects of inbreeding, endogamy, genetic admixture, and outbreeding on human health: a (1001 Dalmatians) study. Croat Med J. 2006;47:601-10. Medline:16909458

30 Campbell H, Carothers AD, Rudan I, Hayward C, Biloglav Z, Barac L, et al. Effects of genome-wide heterozygosity on a range of biomedically relevant human quantitative traits. Hum Mol Genet. 2007;16:233-41. Medline:17220173 doi:10.1093/hmg/ddl473

31 McQuillan R, Leutenegger AL, Abdel-Rahman R, Franklin CS, Pericic M, Barac-Lauc L, et al. Runs of homozygosity in European populations. Am J Hum Genet. 2008;83:359-72. Medline:18760389 doi:10.1016/j.ajhg.2008.08.007

32 Pulanic D, Polasek O, Petrovecki M, Vorko-Jovic A, Pericic M, Barac Lauc L, et al. Effects of isolation and inbreeding on human quantitative traits: An example of biochemical markers of hemostasis and inflammation. Hum Biol. 2008;80:513-33.

33 Rudan I, Carothers AD, Polasek O, Hayward C, Vitart V, Biloglav Z, et al. Quantifying the increase in average human heterozygosity due to urbanisation. Eur J Hum Genet. 2008;16:1097-102. Medline:18322453 doi:10.1038/ejhg.2008.48

34 Polasek O, Kolcic I, Smoljanovic A, Stojanovic D, Grgic M, Ebling B, et al. Demonstrating reduced environmental and genetic diversity in human isolates by analysis of blood lipid levels. Croat Med J. 2006;47:649-55. Medline:16909463

35 Kolcic I, Vorko-Jovic A, Salzer B, Smoljanovic M, Kern J, Vuletic S. Metabolic syndrome in a metapopulation of Croatian island isolates. Croat Med J. 2006;47:585-92. Medline:16909456

36 Vitart V, Rudan I, Hayward C, Gray NK, Floyd J, Palmer CN, et al. SLC2A9 is a newly identified urate transporter influencing serum urate concentration, urate excretion and gout. Nat Genet. 2008;40:437-42. Medline:18327257 doi:10.1038/ng.106

37 Rudan I, Campbell H, Carothers AD, Hastie ND, Wright AF. Contribution of consanguinuity to polygenic and multifactorial diseases. Nat Genet. 2006;38:1224-5. Medline:17072294 doi:10.1038/ng1106-1224

38 Rudan I, Skaric-Juric T, Smolej-Narancic N, Janicijevic B, Rudan D, Klaric IM, et al. Inbreeding and susceptibility to osteoporosis in Croatian island isolates. Coll Antropol. 2004;28:585-601. Medline:15666589

39 Rudan I, Rudan D, Campbell H, Carothers A, Wright A, Smolej-Narancic N, et al. Inbreeding and risk of late onset complex disease. J Med Genet. 2003;40:925-32. Medline:14684692 doi:10.1136/jmg.40.12.925

40 Johansson A, Marroni F, Hayward C, Franklin CS, Kirichenko AV, Jonasson I, et al. Common variants in the JAZF1 gene associated with height identified by linkage and genome-wide association analysis. Hum Mol Genet. 2009;18:373-80. Medline:18952825 doi:10.1093/hmg/ddn350

41 Ivkovic V, Vitart V, Rudan I, Janicijevic B, Smolej-Narancic N, Skaric-Juric T, et al. The Eysenck personality factors: psychometric

structure, reliability, heritability and phenotypic and genetic correlations with psychological distress in an isolated Croatian population. Pers Individ Dif. 2007;42:123-33. doi:10.1016/j.paid.2006.06.025

42 Mutti DO, Cooper ME, O'Brien S, Jones LA, Marazita ML, Murray JC, et al. Candidate gene and locus analysis of myopia. Mol Vis. 2007;13:1012-9. Medline:17653045

43 Wang IJ, Chiang TH, Shih YF, Hsiao CK, Lu SC, Hou YC, et al. The association of single nucleotide polymorphisms in the 5 -regulatory region of the lumican gene with susceptibility to high myopia in Taiwan. Mol Vis. 2006;12:852-7. Medline:16902402

44 Li T, Xiao X, Li S, Xing Y, Guo X, Zhang Q. Evaluation of EGR1 as a candidate gene for high myopia. Mol Vis. 2008;14:1309-12. Medline:18636116

45 Tamm ER, Russell P, Epstein DL, Johnson DH, Piatigorsky J. Modulation of myocilin/TIGR expression in human trabecular meshwork. Invest Ophthalmol Vis Sci. 1999;40:2577-82. Medline:10509652

46 Alward WL, Kwon YH, Khanna CL, Johnson AT, Hayreh SS, Zimmerman MB, et al. Variations in the myocilin gene in patients with open-angle glaucoma. Arch Ophthalmol. 2002;120:1189-97. Medline:12215093

47 Suzuki Y, Iwase A, Araie M, Yamamoto T, Abe H, Shirato S, et al. Risk factors for open-angle glaucoma in a Japanese population: the Tajimi Study. Ophthalmology. 2006;113:1613-7. Medline:16828504 doi:10.1016/j.ophtha.2006.03.059

48 Xu L, Wang Y, Wang S, Wang Y, Jonas JB. High myopia and glaucoma susceptibility the Beijing Eye Study. Ophthalmology. 2007;114:216-20. Medline:17123613 doi:10.1016/j.ophtha.2006.06.050

49 Kawase K, Tomidokoro A, Araie M, Iwase A, Yamamoto T; Tajimi Study Group et al. Ocular and systemic factors related to intraocular pressure in Japanese adults: the Tajimi study. Br J Ophthalmol. 2008;92:1175-9. Medline:18669541 doi:10.1136/bjo.2007.128819

50 Paluru PC, Nallasamy S, Devoto M, Rappaport EF, Young TL. Identification of a novel locus on 2q for autosomal dominant high-grade myopia. Invest Ophthalmol Vis Sci. 2005;46:2300-7. Medline:15980214 doi:10.1167/iovs.04-1423

51 Andrew T, Maniatis N, Carbonaro F, Liew SH, Lau W, Spector TD, et al. Identification and replication of three novel myopia common susceptibility gene loci on chromosome 3q26 using linkage and linkage disequilibrium mapping. PLoS Genet. 2008;4:e1000220. Medline:18846214 doi:10.1371/journal.pgen.1000220

52 Zhang Q, Guo X, Xiao X, Jia X, Li S, Hejtmancik JF. A new locus for autosomal dominant high myopia maps to 4q22-q27 between D4S1578 and D4S1612. Mol Vis. 2005;11:554-60. Medline:16052171

53 Naiglin L, Gazagne C, Dallongeville F, Thalamas C, Idder A, Rascol O, et al. A genome wide scan for familial high myopia suggests a novel locus on chromosome 7q36. J Med Genet. 2002;39:118-24. Medline:11836361 doi:10.1136/jmg.39.2.118

54 Nallasamy S, Paluru PC, Devoto M, Wasserman NF, Zhou J, Young TL. Genetic linkage study of high-grade myopia in a Hutterite population from South Dakota. Mol Vis. 2007;13:229-36. Medline:17327828

55 Young TL, Ronan SM, Alvear AB, Wildenberg SC, Oetting WS, Atwood LD, et al. A second locus for familial high myopia maps to chromosome 12q. Am J Hum Genet. 1998;63:1419-24. Medline:9792869 doi:10.1086/302111

56 Paluru P, Ronan SM, Heon E, Devoto M, Wildenberg SC, Scavello G, et al. New locus for autosomal dominant high myopia maps to the long arm of chromosome 17. Invest Ophthalmol Vis Sci. 2003;44:1830-6. Medline:12714612 doi:10.1167/iovs.02-0697

57 Young TL, Ronan SM, Drahozal LA, Wildenberg SC, Alvear AB, Oetting WS, et al. Evidence that a locus for familial high myopia maps to chromosome 18p. Am J Hum Genet. 1998;63:109-19. Medline:9634508 doi:10.1086/301907

58 Stambolian D, Ibay G, Reider L, Dana D, Moy C, Schlifka M, et al. Genomewide linkage scan for myopia susceptibility loci among Ashkenazi Jewish families shows evidence of linkage on chromosome 22q12. Am J Hum Genet. 2004;75:448-59. Medline:15273935 doi:10.1086/423789

59 Goldstein DB, Cavalleri GL. Genomics: understanding human diversity. Nature. 2005;437:1241-2. Medline:16251937 doi:10.1038/4371241a

60 Didelez V, Sheehan N. Mendelian randomization as an instrumental variable approach to causal inference. Stat Methods Med Res. 2007;16:309-30. Medline:17715159 doi:10.1177/0962280206077743